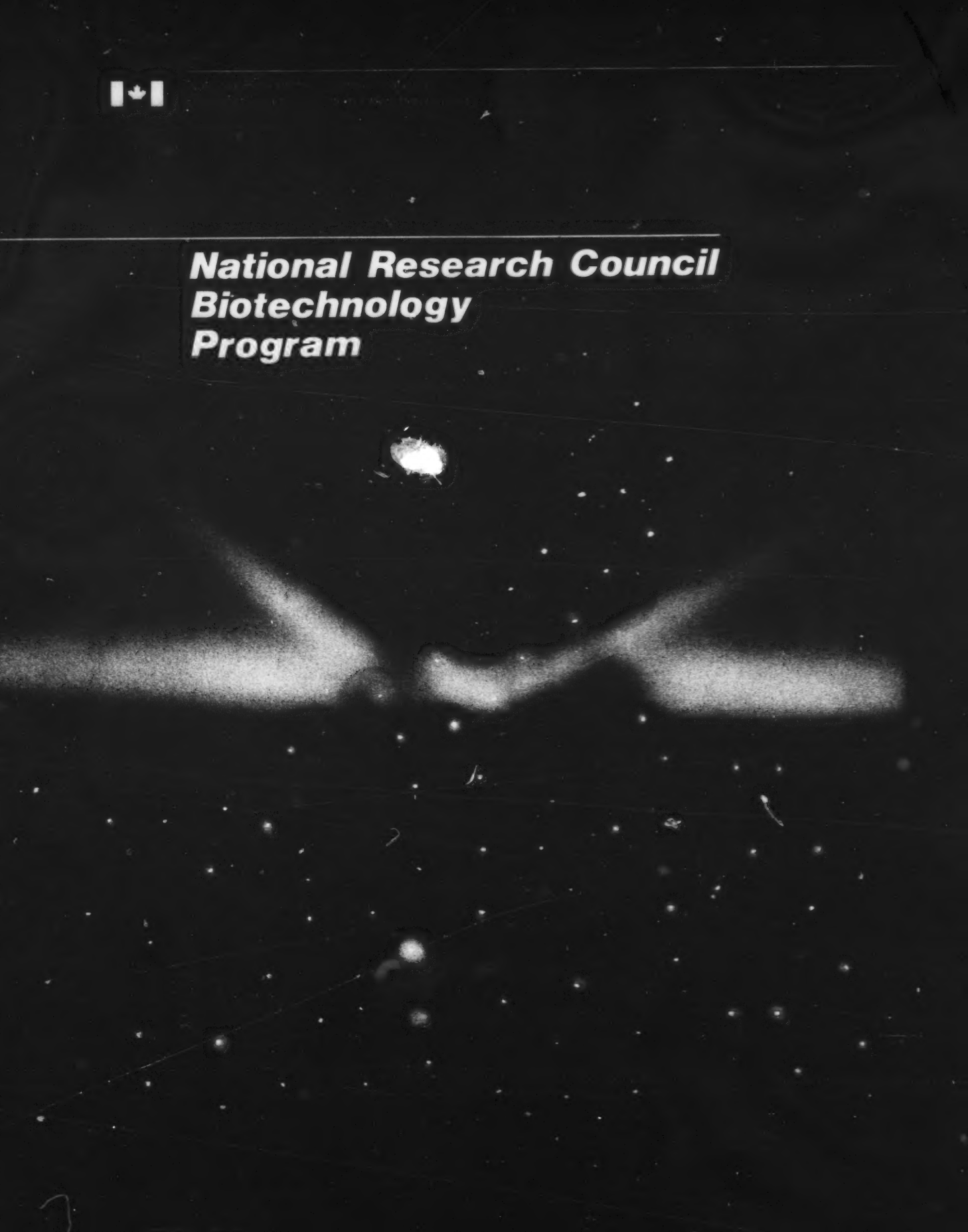
National Research Council
Biotechnology
Program

90-00139/

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I. INTRODUCTION

Around the world, a new economic order based on global competition in knowledge-intensive industries is emerging. Canada is a part of this order and dependent on trade for its survival. The nation exports some $120 billion in merchandise annually, amounting to about 30 percent of the GDP, much of it bulk commodities. The Organization for Economic Cooperation and Development (OECD) estimates that by 1995, fully 25 per cent of world trade will be in high-tech products, double the proportion of the early 1980s.

But Canada has a serious and growing deficit in high technology trade and this is connected to its poor performance in research and development. Canada spends about half the level of its GDP on research and development as do the U.S., Japan, West Germany, or Sweden. Unless we make major improvements in our competitive performance in technology, the country faces economic stagnation and decline. We need to apply new technologies to the revitalization of existing industries and to the development of new ones.

As Canada's national science and technology institution, the National Research Council recognizes the urgent necessity of strengthening the nation's industrial technology. Our objective is to foster Canada's economic development by directing NRC resources primarily towards industrial support. The NRC Biotechnology Program is an expression of this commitment.

Modern biotechnology has been recognized as a strategic technology with applications across a wide range of sectors, including agriculture, food-processing, industrial chemicals, medicine, pharmaceuticals, mining, and forest products.

Biotechnology, simply stated, is the use of living organisms for practical and industrial purposes. It dates from the beginning of civilization in the making of bread, the fermenting of beverages and cheese-making. Today, biotechnology uses a battery of recently developed, powerful scientific tools like genetic engineering, protein engineering, cell fusion, and monoclonal antibody production.

Since 1983, when the federal government designated NRC as the nation's lead agency for biotechnology research and development, we have harnessed much of our life science research capability to a program aimed at sustaining industrial activity, facilitating commercialization, and keeping Canadian companies competitive.

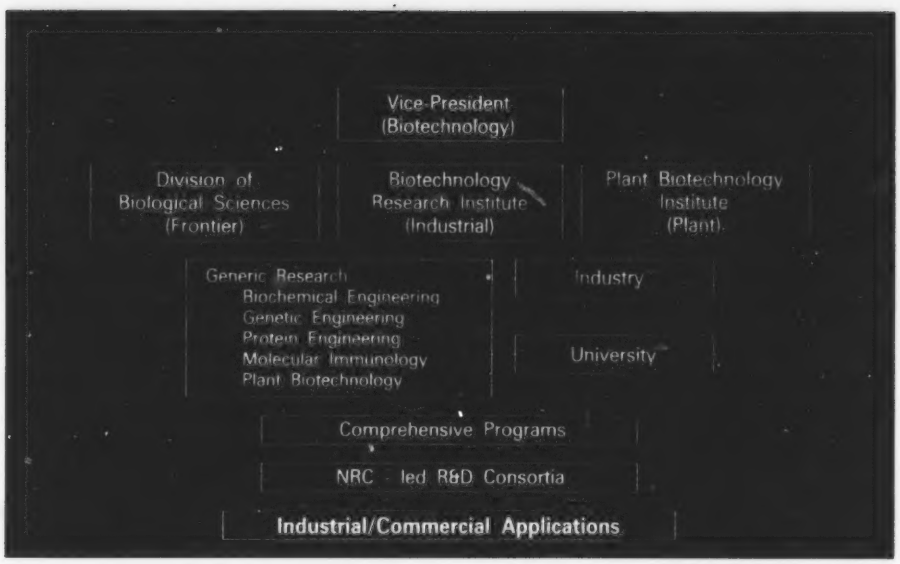
The NRC Biotechnology Program emphasizes applications. It is directed at producing new products and processes, and making current industrial activity more efficient. We sponsor collaborative agreements, research consortia, workshops, and conferences that link industry, universities, and government. Our objective is to remove all barriers and artificial obstacles separating basic and applied research, engineering and advanced technology.

Much has changed since the federal government introduced its National Biotechnology Strategy, a time when our industrial base in biotechnology was practically non-existent. Today, the strategy is working very well, with scientists and engineers now actively engaged in many areas of cooperative research, and our technological capacity in Canada continues to expand and diversify.

This is clearly exemplified at the NRC by the level of physical and human resources we have devoted to biotechnology. There are now more than 200 biotechnology companies moving into the commercial arena in Canada. Their products and processes currently under test are diverse, ranging from the bioleaching of uranium and gold, to the production of human and animal diagnostic kits and vaccines, herbicide-resistant food crops, and a host of other products from biosensors to enzymes for paper production and bacterium-based insecticides.

Canada's future prosperity and its competitiveness in the markets of the 21st century depend on its ability to develop and apply new technologies, both in the creation of new industries and in the strengthening of traditional ones. To capitalize on the momentum Canada has developed in biotechnology, we need to increase the funding devoted to it and strengthen the cooperative bonds that have been forged between industry, government, and the universities. The NRC Biotechnology Program is dedicated to ensuring the full development of biotechnology in Canada.

Dr. Maurice Brossard
Senior Vice-President Laboratories
Vice President (Biotechnology)
National Research Council
January 1989



(A) The Division of Biological Sciences in Ottawa, Ontario.

(B) The Biotechnology Research Institute in Montreal, Quebec.

(C) The Plant Biotechnology Institute in Saskatoon, Saskatchewan.

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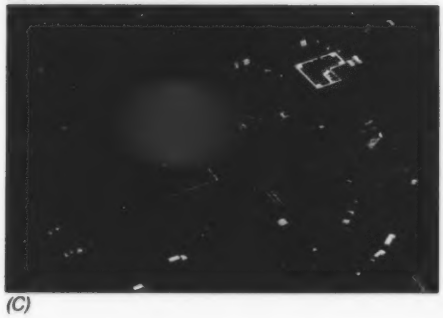

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II. OVERVIEW OF THE NRC BIOTECHNOLOGY PROGRAM

The NRC Biotechnology Program emphasizes strategic or generic research with a broad range of industrial applications. This research approach bridges the gap between basic science and the kind of applied research done in industry to develop specific products. It solves problems associated with the use of technology by industry, in areas such as the development of bioreactors, the engineering of microorganisms for potential products, and the improvement of our understanding of the molecular genetics and biochemistry of industrially important microorganisms.

NRC's research style often leads to a pooling of Canada's science and technology resources in order to benefit from the "critical mass" achieved by such integrated communal endeavours. The Program also encourages the involvement of Canada's biotechnology industries at an early stage, giving them a vital head start, and ensuring that marketplace considerations influence the decision-making process.

The heart of the NRC Biotechnology Program is the leading-edge research and development work performed at the Plant Biotechnology Institute (PBI) in Saskatoon, the Division of Biological Sciences (DBS) in Ottawa, and the Biotechnology Research Institute (BRI) in Montreal. PBI focuses on the biotechnology of plants, DBS performs frontier research, and BRI, the newest biotechnology division, links itself with industry. These three divisions employ over 700 scientists, engineers, and support personnel, and operate with an annual budget of more than $60 million.

While the research carried out by these centres is national in scope and relevance, it is also sensitive to regional needs and concerns. For example, PBI with its emphasis on plant research is located in Canada's agricultural heartland, while BRI, which houses one of the nation's largest facilities for pilot-scale R&D, is located in the centre of Montreal's growing pharmaceutical industry. DBS, committed to frontier research in the life sciences generally, is especially relevant to Ottawa's medical research community.

NRC collaborative efforts include sponsorship of an annual industrial biotechnology conference which brings together the major players in Canada, and leadership of national biotechnology networks involved in forestry and environmental research. A key mechanism for fostering productive collaboration between industry, universities and the NRC labs is a series of Comprehensive Programs in strategic areas of biotechnology such as health care, forestry and agriculture. These Programs are tightly focused on areas of opportunity where Canadians can be expected to take a technological lead and they have objectives that are obtainable within two to five years.

The NRC Biotechnology Program also sponsors Research and Development consortia in strategic areas of biotechnology. One advanced consortium in protein engineering combines university, industry, and NRC researchers and uses the NRC Centre for Protein Structure and Design as its central locus (see page 14). Proteins are the basis of living systems, and their design, modification, and manipulation is considered the way of the future in biotechnology.

III. PLANT BIOTECHNOLOGY INSTITUTE

Plants are Canada's most important resource. Yearly exports of agricultural plants are valued at $7 billion, while forest-product industries are worth more than $20 billion annually.

1. Increasing the resistance of cereals like barley to cold and salt stresses is an important program at the Plant Biotechnology Institute.

The NRC Plant Biotechnology Institute (PBI), located on the campus of the University of Saskatchewan in Saskatoon, is the nation's lead agency for research to improve agricultural, silvicultural, and industrial crop plants. It serves the biotechnology community and industrial sectors involved in growing and processing plants.

Opened in the 1930s, this laboratory was one of the first in Canada to engage in advanced biological technology research, integrating chemistry, cell biology, and engineering in a unique and highly productive way. After the Second World War, as the NRC's Prairie Regional Laboratory, it achieved a string of successes out of proportion to its size; it solved the wheat rust problem in the 1950s; it laid the foundation of canola (rapeseed) as a multi-billion dollar Canadian crop in the mid-1950s; and it did almost all of the pioneering Canadian work in plant cell technology and nitrogen fixation during the 1960s and 1970s.

Twenty five years ago, the laboratory ventured into the artificial culture of plant cells. At the time, few people thought that such technology was even feasible, let alone useful. When biotechnology began gaining recognition as a strategic technology with significant economic potential in the 1970s, the laboratory was prepared with expertise and a record of achievement in the biotechnology of plants.

Today, PBI is the mainspring of plant biotechnology development in Canada and a centre of plant molecular biology research competitive on a world scale. PBI's 150 full-time staff and additional outside researchers concentrate on higher plants, especially those important to Canada's economy such as cereal grains, oilseed plants, legumes, and conifer trees.

The goal is to generate variability in plant cells, producing superior individuals for integration into breeding programs. Plants are sought for their growth and product quality and for resistance to stresses such as cold, herbicides, salinity, drought, insects, and plant disease. This is achieved by the development of innovative techniques for culturing cells, characterizing them, regenerating whole plants, mass producing cells, and genetically manipulating plant genomes to create improved varieties.

PBI combines world-class research focusing on producing applications of benefit to Canada's plant-dependent industries with effective business and outreach programs to collaborators and clients in the marketplace.

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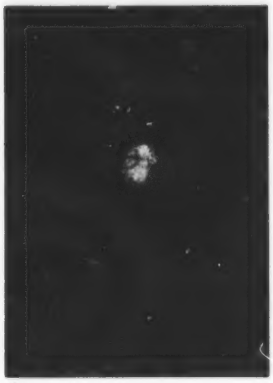

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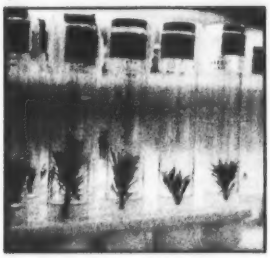

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2. In different pea genotypes, photosynthetic capacity has been found to be related to the activity of RUBISCO, an enzyme involved in both the synthesis and utilization of sugar.

3. Synthetic analogues of natural plant growth regulators speed seed germination in crops like canola, wheat, corn and vegetables, thereby decreasing damage due to frost, herbicides and disease.

4. Cultured cells of Catharanthus roseus (periwinkle) showing the accumulation of alkaloids (white areas) identified as precursors to anti-cancer compounds.

5. Micropropagation of conifers is an important first step towards enabling technologies for improving Canadian forests.

6. The Plant Biotechnology Institute pioneered laboratory techniques for culturing plant cells and inducing them to undergo morphogenesis to mature plants. It is a recognized leader in the field.

Research at PBI

PBI's research program is divided into three major areas: Cell Technology, Gene Technology, and Biological Chemistry. These research areas are closely intertwined at the Institute, forming a natural grouping of research skills that are vital to ensuring the competitiveness of the large sector of Canada's economy that depends on plants. A Board of Governors, made up of experts from industry and the universities, provide advice and guidance on the relevance of PBI's program.

1. Cell Technology Laboratory

Cell Technology concentrates on growing plant cells in the laboratory. These *in vitro* techniques are useful in crop and conifer tree improvement, and include research on isolating specific cell types, mass producing or cloning of cells, and manipulating plant cell genetic make-up.

Tissue culture methods have led to wheat plants with heritable, improved tolerance to cold, and to barley with improved salt tolerance. Seedlings of Douglas fir, white spruce, and western white pine have been produced in the laboratory from the bud tissues of older trees (when desirable factors such as disease resistance and straightness are evident). Improvements to the technology for producing a multitude of embryos has recently opened the way to the large-scale micropropagation and genetic engineering of conifers.

2. Gene Technology Laboratory

This lab focuses on techniques for introducing desirable genes into plant cells. It utilizes DNA/RNA molecular techniques such as analysis, synthesis, transfer, expression and cloning, with an emphasis on oilseeds, cereals, legumes, and conifers.

Bacillus thuringiensis toxin genes have been successfully introduced into tobacco and rapeseed cells, the goal being to make crops insect-resistant at the gene level. Work on plant productivity genes concentrates on two systems in green plants, photosynthesis and nitrogen fixation. The rhizobial bacteria that infect legumes, making nitrogen fixation possible, are the subject of genetic engineering studies.

3. Biological Chemistry Laboratory

Scientists in this lab are working to control plant metabolism by chemical and biochemical techniques. Projects are underway to alter the biochemical pathways in oilseed plants like canola, to improve lipid quality, and to suppress unwanted chemical products like erucic acid and the glucosinolates. Market interest in this work stems from the value of oil quality over mere quantity.

The production of pharmaceutically important phytochemicals by *in vitro* cell systems has led to a market for sanguinarine, an alkaloid with antibiotic properties derived from poppy cell cultures. A U.S. pharmaceutical company is setting up a plant in Canada to scale the NRC system up for industrial production. Another

alkaloid of interest is catharanthine, a component of the anti-cancer drug, vinblastine, derived from periwinkle cell cultures. The process for the semi-continuous production of these valued plant cell metabolites using "elicitor" substances is now subject to patent applications in Canada, Japan, the European Economic Community, and other countries.

PBI's Outreach Program

PBI has an external program to ensure that its technology is effectively transferred to industry. The program fosters linkages between PBI researchers and their counterparts in industry and academia across Canada. Under the Institute's Guest Researcher program more than 70 scientists and technicians use PBI's on-site facilities each year and participate in PBI projects. The Affiliated Scientist program brings together top performers in Canadian biotechnology to meet and share ideas on new frontiers in plant biotechnology. PBI guarantees a place in the Saskatoon labs for any Affiliated Scientist who wants to visit and spend time working with one of the project groups. The Invited Graduate Student program makes the Institute available to universities across Canada for thesis research. The Institute encourages and is currently active in collaborative research at the project level with several government research laboratories, notably Agriculture Canada. It is also engaged in research partnerships with many private corporations, ranging from one-on-one contracting, to joint ventures for performance of specific research, and to straightforward licensing agreements.

PBI's Plant Biotechnology Fund provides for contracting-out of parts of PBI research projects to other established Canadian laboratories. Proposal competitions are held each winter with a technical committee overseeing the awards and keeping track of the projects.

Examples of the many research projects include a program with Biotechnica Canada on oilseed lipid quality improvement, a joint venture with Vipont Laboratories on plant cell bioreactor production of the antibiotic sanguinarine, and a four-year project with the Saskatchewan Wheat Pool on enhancing cold tolerance in wheat and regeneration of selected wheat cells.

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7. The yellow nodules are wheat embryos generated from somatic cells in culture. The research aims at producing wheat crops with greater resistance to environmental stresses.

8. Molecular geneticists at PBI transfer genes of value into plant cells by first inserting them into strains of Agrobacterium which are natural infectious agents of plants.

9. Recombinant DNA technology used to transform plant cells is a relatively new area and promises powerful tools for crop improvement.

IV. DIVISION OF BIOLOGICAL SCIENCES

In 1936, the British philosopher-scientist Sir Julian Huxley pronounced that biology's applied cousin — biotechnology — would in the long run be more important than the applications from the sciences of 'lifeless matter'. This confidence in the practical potential of research into living systems has since been widely shared, and represents one of the driving forces within the NRC's Division of Biological Sciences. From its beginnings over six decades ago as the Division of Economic Biology and Agriculture, this first Canadian biotechnology laboratory has enjoyed a long, successful history of applying state-of-the-art research to industrial concerns and problems.

10 Two-dimensional NMR reveals the structure of proteins in solution

The Division was a Canadian leader in developing molecular genetics to a high level of expertise (resulting in one of the first industrial uses of genetic engineering) and it successfully transferred its technologies for preserving food and treating organic waste effluents to industry. The pioneering applications of NMR spectroscopy to the study of biological systems by DBS biophysicists has opened 'real time' windows on cell metabolism and led to new, rapid techniques of disease diagnosis. A Division laboratory working with cell-surface carbohydrates and their immunological properties has established an international reputation for developing human and veterinary diagnostics and vaccines.

These applications have grown out of the high quality frontier research done at DBS over the years. The calibre of this work is reflected in the Division's large number of scientific publications, in its interactions with prestigious international institutions, and the number of its scientists who have gone on to develop the biochemical and biological laboratories of Canada's universities and industries. Many of DBS's scientists currently serve as adjunct professors at Canadian and U.S. universities.

DBS researchers are a diverse group — chemists, physicists, biologists, geneticists, biochemists, microbiologists, computer experts, mathematicians, and engineers. This diversity permits the Division to structure its programs along interdisciplinary lines, accessing the strength inherent in multi-talented groups focussed on common research problems.

Research at DBS

Upwards of 250 scientists, engineers and support staff work at DBS. About 170 of these are full time NRC employees, while the remainder are term research associates, visiting scientists, postdoctoral fellows, and university graduate students. The direction of research projects is determined by the considerations and interest of outside industries and universities, with over 40 companies maintaining significant contacts and upwards of a dozen industrial labs linked to the Division through the NRC's Industrial Research Assistance Pro-

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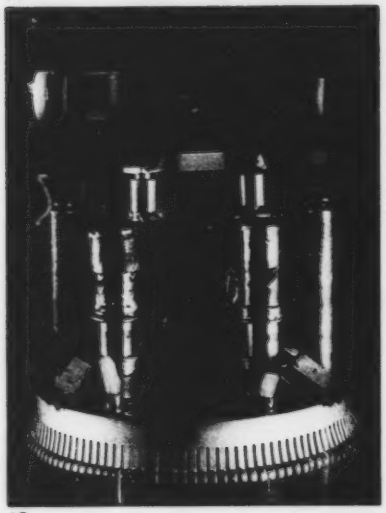

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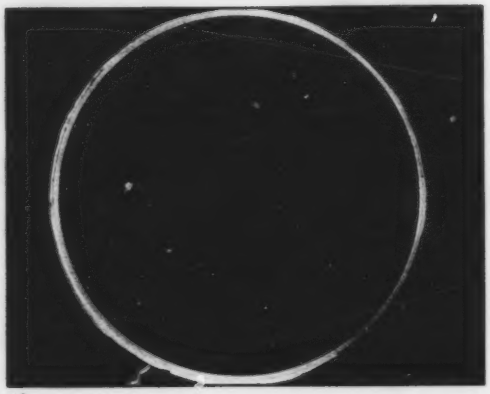

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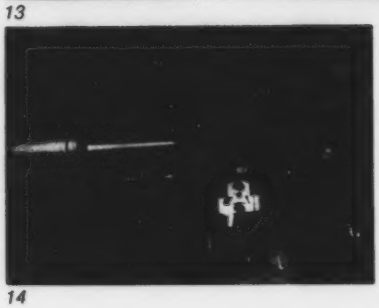

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11. Fluorescence spectroscopy reveals how proteins and other large biomolecules change shape as the environment is modified.

12. NRC biophysicists design their own probes for examining living tissue.

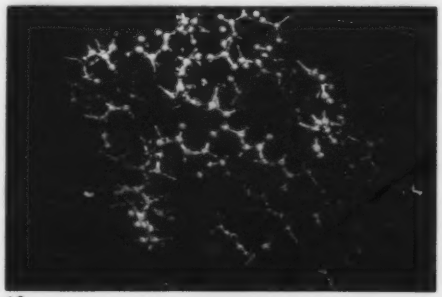
13. Bio-typing bacterial strains. DNAase produced by this bacterium (red streak) breaks down DNA-labelled toluidine blue in the agar.

14. X-ray crystallography provides detailed information on the 3-dimensional structures of proteins and polypeptides.

gram. There is a strong curiosity-oriented component to DBS's research style, but economic pay-off continues to be a key consideration, with most of the work falling into one of the priority areas of the Division: health and pharmaceuticals; food and beverages; agricultural and forestry resources; chemicals and fine chemicals.

15. NRC's Dr Saran Narang, one of the genetic architects who synthesized the gene for proinsulin, the precursor of the hormone for treating diabetics.

The Division is divided into large laboratories that bring together research projects under three major themes — health care research, carbohydrates, and proteins. Much of the latter laboratory's activities are integrated into a larger, interdivisional Centre for Protein Structure and Design (see page 14), the pivotal element in NRC's protein engineering programs and a vital link with Canadian industries and universities wanting to enter the field or expand existing programs.



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16. Molecular model of oncomodulin, a calcium-binding protein that shows up in cancer and fetal cells.

1. Protein Laboratory

It is difficult to overstate the importance of proteins in living systems. They exchange the cell's gases, protect it from invasion, manage and modulate its gene expression, make up a vast intercellular communications system, and they stitch together the immensely complex tapestry of intermediary metabolism. The future of biotechnology lies in understanding these molecules — what they do, how their structures allow them to do these things, what modifications improve their function, and how they can be produced on an industrial scale. Just one biotechnologically produced protein, the so-called 'blockbuster' drug Tissue Plasminogen Activator (TPA), now nets pharmaceutical companies hundreds of millions of dollars annually.

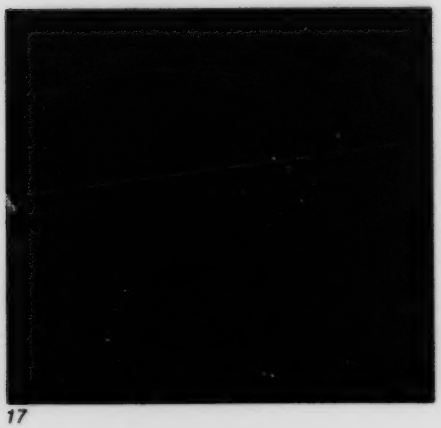
DBS has a special blend of expertise in its protein laboratory to work in this field, with specialists in molecular genetics, NMR, Raman, and fluorescence spectroscopies, protein chemistry, enzymology, X-ray crystallography, and mathematical modelling. This range of techniques permits DBS researchers to isolate specific proteins, determine their structure and other characteristics, make changes at precise sites on the protein (based on data from modelling and protein chemistry), and harvest the redesigned protein for analysis. This technology is leading to a host of novel and improved enzymes, hormones, blood factors and other proteins of economic value. One area of DBS's attention is industrially important enzymes that break down carbohydrates (glycosidases). These include enzymes that degrade cellulose and hemicellulose of impor-

tance to the pulp and paper industry, and amylases that interest the brewing industry. The focus is also on protein-degrading enzymes such as the family of cysteine proteases, notably papain. The rational design of inhibitors to these enzymes has important implications for certain human disease therapies. There are other, specialty molecules of interest to DBS, such as the insecticide proteins produced by *Bacillus thuringiensis* (the Bt proteins are the most important of the natural commercial toxins against spruce budworm), and synthetic human parathyroid hormone, a polypeptide with great potential for reversing the effects of osteoporosis.

2. Carbohydrate Laboratory

Bioscientists investigate a range of carbohydrates: the antigenic surface structures on cells, bacteria and viruses fundamental to developing diagnostics and vaccines against disease; plant polysaccharides that yield valued, enzyme-modified products; fuels, flavours and fragrances produced by microbes; and bioreactor designs that enhance biotechnological processes.

Immunochemists in the group have won international recognition for their achievements in bringing the rigors of chemical analysis to the field of immunology. They specialize in interpreting the antigen-antibody interactions underlying the immune response in terms of its biochemical properties and molecular structures. Their novel solutions to long-time, vexing problems in clinical and veterinary microbiology have resulted in a number of socially and economically significant projects that have been transferred to Canadian industries for exploitation. Cell surface carbohydrate antigens have been modified to produce a new generation of vaccines to diseases such as meningitis, gonorrhea, and enteric diseases caused by salmonella and E. coli. In the veterinary field, antigen structure research combined with monoclonal antibody techniques have led to rapid diagnostic tests for diseases like brucellosis in cattle and pleuropneumonia in swine, both of which are now being exploited by industry.



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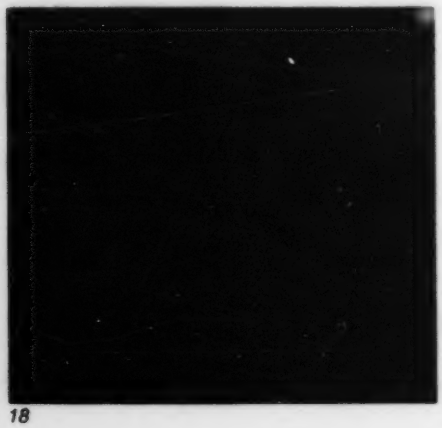

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17, 18. A synthetic antigen (green) moves into the waiting maw of an antibody arm. Computer graphics help NRC immunochemists to understand the immune response at the molecular level.

Designing New Proteins

NRC Centre for Protein Structure and Design

NRC's interdivisional Centre for Protein Structure and Design is a matrix of techniques and expertise drawn from the Division of Biological Sciences and the Biotechnology Research Institute. Located in Ottawa and Montreal, the Centre is pivotal to one of biotechnology's most important new areas — protein engineering.

For Canada's private sector, the potential benefits of this technology are enormous, with new protein and polypeptide products for the pharmaceutical, food, agricultural, forest, and waste management industries.

Proteins are engineered — or redesigned — by first isolating them in a pure form, determining their structures, and then remodelling them.

8. The modified gene is inserted into a microorganism for production of the new, rationally redesigned protein.

1. Molecular geneticists at PBI, DBS, and BRI have the technology to synthesize the DNA sequence that codes for a protein (an enzyme is a good example) and then to insert this gene into a bacterium or yeast.

9. The loop repeats, with the structure and character of the new protein examined for changes, tested against predictions, and so on. In this way, new proteins and polypeptides are born.

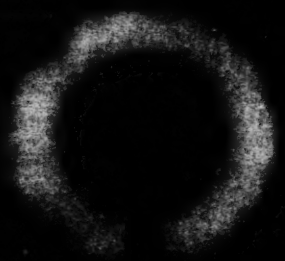
2. Microbiologists induce the transformed microorganism to express the gene, thereby producing the protein.

3. Protein Chemists characterize the product and help produce crystals of the molecule.

This suggests specific design changes to the amino acid architecture of the molecule that will improve it, such as new uses, ability to function at higher or lower temperatures or pH, and so on. Molecular modellers at DBS and BRI play important roles here.

7. Molecular geneticists make precise changes to the protein gene that will substitute a specific amino acid into the molecule, changing its structure and perhaps its biological behaviour.

5. **The accumulated knowledge of the protein's structure and how this determines its function, its sensitivity to temperature, pH, etc. is brought into play.**



X-ray crystallographers at DBS determine the three-dimensional structure of the protein in the crystals. The structures of smaller proteins in solution is revealed using BRI's two dimensional NMR technology.

The advantages to food producers of labelling products as 'natural' has led to microbial techniques for producing flavour compounds (notably acetaldehyde) and the development of bioreactor processes for large scale production. Brewing yeasts have been genetically modified to increase their ability to break down large polysaccharides and ferment the resulting sugars down to alcohol. Enzyme systems are being produced to more efficiently degrade various, edible polysaccharides and to improve pulp and paper making. DBS's long standing expertise in the treatment of agricultural and industrial wastes rests on a knowledge of anaerobic bacteria (in particular the methanogens) and bioreactor systems that harness the capacities of these microorganisms on large scales. In collaboration with BRI, studies of pulp and paper waste water treatment using anaerobic bioreactors are under way.

19. Mammalian metabolism can be studied directly using nuclear magnetic resonance spectroscopy without harm to the test animal.

20. Cloned hybridoma cells growing in agar.

21. Papain, with a peptide inhibitor (color), in the enzyme's active site.

20

3. Medical Biosciences

Researchers in this laboratory have established themselves at the leading edge of the quest to define living structures and processes in molecular terms, and to mobilize this knowledge in the fight to understand, diagnose and control human disease. A key element in the group's long range goals is the containment of health care costs through better understanding and new technology.

The laboratory's expertise in measuring metabolic phenomena and diagnosing disease rests on a considerable body of biomedical data gathered over the years — information on plasma membrane structures, their interactions with substances like anaesthetics, antibiotics, and antibodies, and studies of the mechanisms that control cell proliferation.

NMR imaging and spectroscopy are central to the research effort. The approach is diverse, ranging from metabolic evaluations of hearts slated for transplant, to tissue models for measuring drug effects, tests for alcoholic liver disease, and the development of non-invasive

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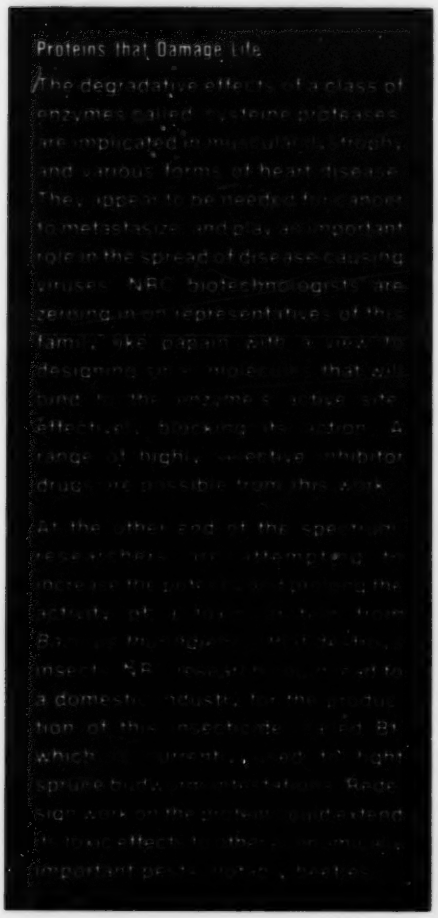
blood sampling techniques for the early detection of cancer. The group's skills at localized NMR imaging has led to probe designs that are currently being marketed by a private company.

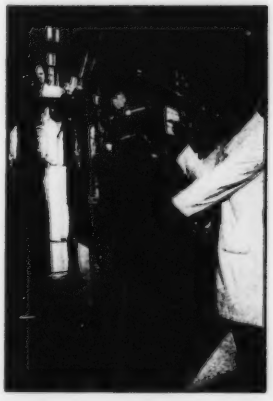
Over two decades of research has revealed that disturbances in a vital signalling mechanism on the cell membrane lies at the heart of cancer. The calcium-dependent system is involved in turning on chromosome replication and researchers are seeking an understanding of how certain cancer-causing agents override these sensitive controls. The laboratory is also looking at the biological function and diagnostic potential of oncomodulin, an unusual calcium-binding protein they discovered that is specific to cancer cells and quasi-metastatic embryonic tissue.



Industry-University Linkages

Like the other two biotechnology divisions, DBS has developed an extensive system of contacts and cooperative research programs with industry and the universities. Its three main laboratories have established joint ventures with outside agencies across the country in a number of biological disciplines: specialized NMR probes for examining living systems in Ottawa; genetically transformed yeast for producing human parathyroid hormone in Toronto; diagnostic kits for animal diseases in Saskatoon; specialized antibodies for disease diagnosis and blood cancer markers in Edmonton.

The Division participates in focused, shorter term research programs that include other biotechnology divisions and industries, and like PBI and BRI it provides laboratory facilities to companies at the start-up phase of research. DBS has long established relationships with well known universities, teaching hospitals and research institutes in Canada and around the world. Its visiting scientists and postdoctoral students often come from these institutions on exchange programs with Divisional scientists and engineers.



22. DBS has a containment facility for large scale production of pathogenic bacterial cells.

V. BIOTECHNOLOGY RESEARCH INSTITUTE

Opened in 1987, the Biotechnology Research Institute (BRI) in Montreal is the newest and largest of NRC's biotechnology laboratories. With a floor space of almost 19000 square meters, the triangle-shaped building is located in the city's 'cité scientifique' site to the northwest on Royalmount Avenue. The blue, burgundy-trimmed edifice cost upwards of $60 million to build and equip, and features one of the largest pilot plants in Canada.

23. What looks like breakfast at BRI is actually different forms of a support medium for immobilizing lipid-degrading enzymes. By reducing the water environment around the enzyme, it reverses its normal direction and builds rather than breaks lipid molecules.

From the outset of its existence in 1984 at temporary premises in downtown Montreal's Royal Victoria Hospital, BRI's aim has been to perform R&D in biotechnology with clear industrial applications. Many projects are chosen in direct consultation with industry, performed in cooperation with industrial partners, or selected to foster the transfer and scale-up of results to industry. Other projects focus on generic research aimed at underpinning industrial technologies.

BRI's pilot plant gives Canadian industry unique access to technical expertise and state-of-the-art equipment. Researchers can scale up fermentation processes through a series of fully automated fermentors, and investigate separation and purification processes using leading-edge biochemical engineering equipment.

The Institute's Board of Governors plays an important role in making its major policy decisions. Seven members of the twelve-member Board, the majority, are from Canada's industrial sector.

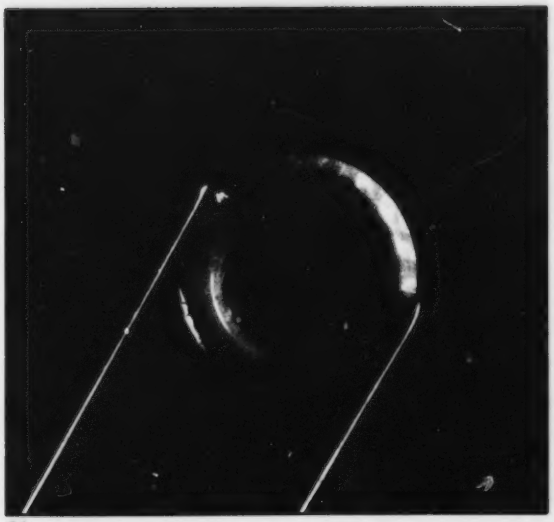
BRI has some 240 NRC personnel and about 60 engineers, scientists and graduate students from industry and universities working in its laboratories and offices. Although relatively new, the Institute is already involved in dozens of joint projects with industry and university partners in areas such as biosensor development, vaccine production, anaerobic waste water purification systems, computer programs for protein design, and the culture of plant and mammalian cells.

Research at BRI

1. Genetic Engineering

This group maintains world-class expertise in the enabling technologies of molecular genetics that form the basis of modern biotechnology: gene synthesis, gene expression, and the genetic manipulation of host-vector systems.

The Genetic Engineering section has five component groups that address major areas of interest in molecular genetics. The first, fundamental group synthesizes DNA and develops the knowledge and tools for inserting and expressing genes in living systems. The other groups focus on life at increasing levels of sophistication: the virology group concentrates on viral/mammalian and viral/insect systems that produce high levels of foreign proteins; the prokaryotic cell group looks at bacterial genetic expression systems with a view to producing industrially important proteins and polypeptides; the yeast group uses recombinant DNA techniques to induce industrially important yeast strains to produce valued proteins and other compounds; and the



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24. The membrane of a biosensor, its window on the outside world.

25. BRI biochemical engineers use computers for real-time monitoring of fermentation processes.

26. Eukaryotic cells (insect) being cultured at BRI.

mammalian cell group focuses on developing new gene expression systems and culture techniques for mammalian cells because of their unique ability to produce proteins of medical importance.

27. These insect cells are infected by viruses carrying valued genes that code for proteins used in medical therapy and diagnosis.

The group has developed a genetic fingerprinting method that promises to lead to applications in police forensic investigations. The method has already helped one Canadian company resolve questions concerning the ownership of yeast strains. Virologists have developed a virus/insect cell system for the production of a wide variety of proteins, notably those that form the basis of veterinary vaccines. A Canadian company is currently working with the Institute to exploit these results. In another program, genes for the insecticide produced by *Bacillus thuringiensis* have been completely defined, and efforts are underway to determine the regions of the gene responsible for toxicity and sensitivity to sunlight. In collaboration with PBI, molecular geneticists are constructing new varieties of crop plants and conifers resistant to specific insect pests. Institute molecular geneticists have identified the genes for proteins in yeast that transmit hormone signals received by cell surface receptors. Pharmaceutical company interest stems from the fact that these signal pathways are similar to those in mammalian cells, opening up new possibilities for regulating the effects of hormones and other signal molecules that control and modulate cell behaviour.

2. Protein Engineering

A core of expertise in protein chemistry, peptide synthesis, and enzymology exists in this section. Central to the section is the protein chemistry group whose specialties are the purification of proteins, the determination of their amino acid sequences and other information on their structures. An enzymology group looks at enzymes, the living system's vital catalytic agents. Another group looks at small chains of amino acids — peptides — many of which have important biological activities. Proteins embedded in plasma membranes that act as receptors for such things as hormones, drugs, toxins, growth factors and neurotransmitters are a focus of interest. Finally, a crystallographic group looks at the shapes proteins assume in space, a characteristic vital to their biological functions.

This section investigates a range of enzyme activities — ligninases in the degradation of wood lignin, lipases in organic environments that cause lipid synthesis rather than breakdown, and immobilized enzymes for efficient, large-scale processing of substrates. In cooperation with genetic engineers, the group designs inhibitors that interfere with enzymes implicated in disease. Structure-function relationships in enzymes, cell surface receptors, and antigen-antibody reactions are a key element in the section's research program. Like the Protein Laboratory at DBS, the section is a major player in the interdivisional Centre for Protein Structure and Design (see page 14).

3. Molecular Immunology

Still the fledgling section of BRI, Molecular Immunology focuses on the market potential of products that derive from hybridoma technology's capacity to produce large quantities of homogeneous antibody. Because of the high specificity of antibodies, they are finding widespread medical applications as therapeutic agents, assay and purification tools, detection devices, and structural probes. The group's initial interests, for which there is already considerable industrial interest, is in techniques for characterizing and sorting cells of the immune system and isolating very large DNA molecules.

4. Biochemical Engineering

This section is the most applied of any biotechnology group within NRC, converting the theoretical findings of basic research to industrial applications. It is here that potential economic value is assessed, where smaller, bench-top processes are put to the critical test of working at larger masses and volumes. Scientific advances in genetic and protein engineering enter the wider, larger arenas of the engineer, leading to marketable products. This group is unique in the life sciences with its high concentration of chemical and biochemical engineers who, along with microbiologists, chemists and biologists, operate a pilot plant where biological processes are subjected to industrial considerations. Research findings are put to the test at larger scales, where mass transfer, shear forces, and other factors come into play. Problems not in evidence at the laboratory bench are revealed here — the optimization of nutrient requirements, the sterility of systems, the separation and purification of products, and the safe disposal of waste effluents. Bioreactors are designed, built, and tested in the production chain of the pilot plant. Computerized systems for monitoring, controlling, and optimizing the design of bioreactors are developed and investigated.

The areas of research interest include the downstream processing and detoxification of solid wastes; the use of lipases in synthetic reactions; the large volume production of plant and mammalian cells; and the development of sensitive but rugged biosensors for monitoring biological processes.

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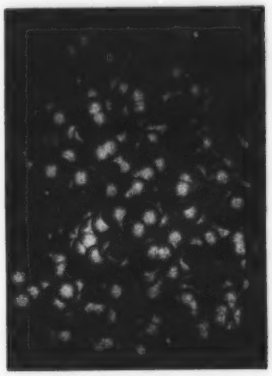

28. Papain, showing its active site cleft. This enzyme belongs to a family of cysteine proteases implicated in a number of human diseases.

29. Genetic engineers examine an autoradiogram of DNA fragments from a B. thuringiensis gene coding for an important insecticide.

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30, 31, 32, 33. The monitoring and evaluation of scaled-up biotechnological processes takes place in the Biotechnology Research Institute's pilot plant, one of the largest of its kind in Canada.

External Programs at BRI

Because of its emphasis on industrial applications and technology transfer, BRI has a major program that aims at establishing collaborative R&D linkages with laboratories in industry and the universities.

The Institute enters into a number of cooperative research arrangements with outside agencies, from straightforward leasing of laboratory space and equipment to 'contract-in' agreements where BRI is hired to do research by industrial clients. In between there are a range of joint-venture contracts preferred by the Institute in which project funding and tasks are shared.

At BRI, an industry can rent laboratory space adjoining the Institute's research wing to pursue research ideas at their beginning or 'incubation' stages, it can send its researchers into Institute labs to do cooperative research, or it can contract to use the Pilot Plant laboratories for scale-up studies. In fact, much of BRI's interactive research with industry involves the Pilot Plant, a facility designed for use by all Canadian biotechnology laboratories interested in scaling up biological processes (see Pilot Plant above).

BRI's list of industrial collaborations takes in companies across Canada, from a Montreal project on PCB biodegradation, to Toronto research on improving yeast strains and, further west, to vaccine production work in Saskatoon.

BRI also administers a program of direct grants or contributions to industrial laboratories to do research that the National Research Council judges to be of value to Canadian biotechnology. The program, which involves all three biotechnology divisions, has NRC contributing funds to industrial labs to carry out one part of a project while NRC does the other in its own laboratories.

34. To determine the 3-dimensional structures of proteins, X-ray crystallographers need crystals of these important biological molecules.

VI. JOINT PROGRAMS AND STRATEGIC PARTNERSHIPS

NRC's mission is to achieve national goals in biotechnology by integrating the efforts of Council laboratories and by collaborating with industry, universities, and other research organizations. Resources must be focused in specific areas to give Canada the critical mass of minds and materials needed to succeed in biotechnology and compete with other industrialized countries.

35. Purified, high-value biomolecules from recombinant DNA technology will underpin tomorrow's pharmaceutical industry.

36. Agricultural biotechnology is leading to better quality crops with increased resistance to stress.

Comprehensive Programs

These programs are designed to lead to a marketable product for a Canadian company within a time-frame acceptable to industry (two to five years). They are tightly focused, include laboratories from Canada's biotechnology industries, universities or other outside agencies, and concentrate in areas where Canadians can be expected to take a technological lead.

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Comprehensive Programs link the scientists and engineers of NRC biotechnology labs together in integrated, communal endeavours that provide the "critical mass" needed to pursue biotechnology's national goals. They enjoy the enthusiastic support of Canadian industries, which often find such research activities too expensive or risky to do alone. Equally important, industry's early involvement in the research gives them a vital head start on their international competitors, and ensures that market considerations strongly influence the research directions.

The NRC has a number of well-planned Comprehensive Programs involving the efforts of over a hundred scientists and engineers from NRC, industries and universities. The Programs are in areas of biotechnology identified as strategic: health, food and agriculture, forestry, and the environment. They include:

- the study of lipid-modifying enzymes in plants aimed at upgrading oil quality;
- research into an anaerobic bioreactor for cleaning up pulp and paper mill effluents;
- the design of inhibitors for enzymes implicated in diseases;
- a bioreactor for the scaled-up production of plant cell metabolites; and,
- a project aimed at optimizing the potency and increasing the lifetime of an insecticide from *Bacillus thuringiensis*.

NRC-Industry-University Networks in Biotechnology

The federal government's National Biotechnology Strategy, established in 1983, identified a number of strategic areas in biotechnology: forestry; waste treatment; agriculture; health care; mineral leaching/metal recovery; and marine biotechnology. In each area a Network was established to promote communication among industrial, university and government labs and to establish cooperative projects to benefit Canada's biotechnology companies.

NRC has played a coordinating as well as an extensive research role in three of these:

BIOFOR, established to link together research efforts in the forest sector; BIOCIDE, a broadly based research project to improve and stabilize an insecticide from *B. thuringiensis*, and ultimately to produce the toxin commercially in Canada; and BIOQUAL, aimed at networking research activities to preserve the quality of the environment.

NRC Industrial Biotechnology Conference

To stimulate communication and networking among the major industrial, university and government players in Canadian biotechnology, the NRC hosts an annual conference on industrial biotechnology.

The conference program includes speakers who cover the broad range of Canada's commercial endeavors in the science, from agriculture and forestry, through pharmaceuticals and health to waste treatment and mineral leaching. It attracts participants who have a stake in this burgeoning international area of technology — industrialists on the hunt for new products or processes, research administrators interested in transferring their technology, government funders of R&D, policy advisors concerned with biotechnology's central issues, and researchers looking to market laboratory advances.

37. Improving the oil quality of canola, a crop second only to cereals in Canada's export sales, requires a better understanding of its genetic make-up.

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38. Genetic engineering at the Montreal Biotechnology Research Institute.

VII. FUTURE DIRECTIONS FOR THE BIOTECHNOLOGY PROGRAM

NRC's Biotechnology Program is firmly committed to fostering Canada's economic development. It does this by responding to the needs of the private sector, by evaluating NRC research activities in terms of their usefulness, and by favouring programs that have industrial clients for their output.

39. The Division of Biological Sciences has an advanced containment facility for doing recombinant DNA research.

40. Ultraviolet light picks up large DNA fragments separated by pulse gel electrophoresis. Mapping and sequencing large genomes will depend on such technologies.

The context in which research is being carried out has evolved dramatically, and nowhere is this more true than in biotechnology. Increasingly, major scientific and technological advances are the result of joint ventures and research consortia. Progress is based on exchanging information, participating in joint projects, and sharing ideas. Thus, the NRC Biotechnology Program is strengthening scientific cooperation with industry and the universities. NRC-led R&D Consortia in biotechnology are a major step in forging these links. The world laboratories currently at the leading edge of biotechnology share a common feature — they are multidisciplinary, composed of scientists and engineers from several disciplines attacking research problems on a number of different but integrated fronts. To compete against American, European and Japanese laboratories, Canada must achieve the same kind of 'critical mass' in its research, focusing on specific, strategic areas of biotechnology. One of these, protein engineering, is well advanced with a consortium forming around the NRC Centre for Protein Structure and Design. Similar Consortia in areas such as bioprocess engineering and plant biotechnology are possibilities for the future.

The NRC effort to disseminate new and more competitive technologies can only be successful, however, with the active participation of industry. Close cooperation between Canada's business and its scientific and technological communities is vital if the country is to acquire the advanced technology it needs to remain competitive in today's global economy. Competing in the international arena demands that Canada deploy all of its economic, scientific, and technological resources to their best advantage.

The NRC Biotechnology Program is a valuable asset in this economic struggle. NRC has the expertise, the facilities, and the will to ensure that Canadian industry receives needed support in this strategic area of technology. It is ready to help Canadian industry take up the challenge of global competition. The accelerating pace of technological change has made this one of the most exciting and promising ages in human history. Canada has the opportunity to play an active part in the global economy, and to secure its future as a dynamic international competitor.

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41. Low temperature research at the Montreal Biotechnology Research Institute.

42. Molecular modelling studies at the Division of Biological Sciences.

43. Chromosome-doubled homozygous barley, produced by cell culture techniques at the Plant Biotechnology Institute.

Further Information:

The NRC welcomes inquiries from outside agencies interested in the Biotechnology Program.

Telephone or write to:

- Coordinator

Biotechnology Program (613) 993-7630

- Communications Manager

Biotechnology Program (613) 993-7659

National Research Council of Canada
Ottawa, Ontario.
K1A 0R6

- Industrial Liaison Officer

Division of Biological Sciences
National Research Council of Canada
100 Sussex Drive
Ottawa, Ontario.
K1A 0R6 (613) 990-0884

- Industrial Liaison Officer

Plant Biotechnology Institute
National Research Council of Canada
110 Gymnasium Road
Saskatoon, Saskatchewan
S7N 0W9 (306) 975-5570

- Industrial Liaison Officer

Biotechnology Research Institute
National Research Council of Canada
6100 Royalmount Avenue
Montreal, Quebec
H4P 2R2 (514) 496-6105

Editor: Wayne Campbell, NRC Biotechnology Program
Writers: Paul Tisdall, the Network/Wayne Campbell
Design: Carisse Graphic Design Ltd.
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